

Viral duality: Regulation of cell immortality in cervical cancer (2014)

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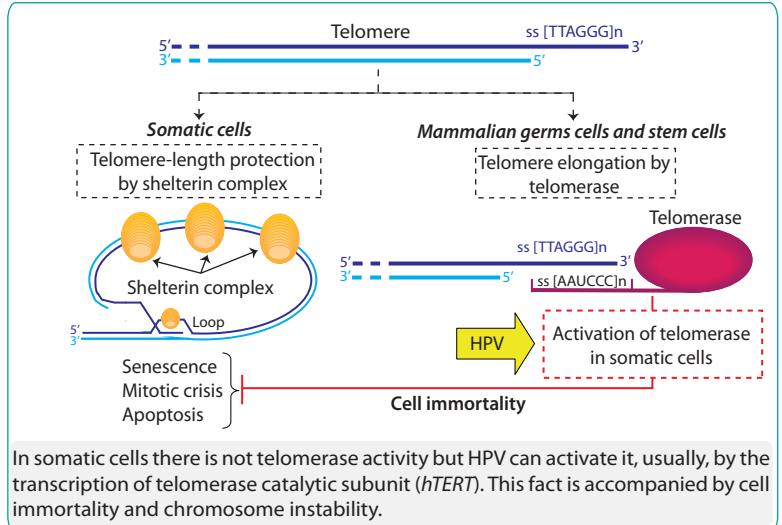
Introduction

Cervical cancer is the third most common cancer in women (8%). It is formed in tissues of the cervix, which connects the uterus and vagina. More than 70% of cervical cancers are caused by Human Papilloma Virus (HPV) infections. Usually, this cancer grows slowly and with surgery it is eradicated. However, due to the latent HPV infections there are many cases of relapse.

HPV has developed multiple strategies to evade immune system and to persist in the host cell. It is specialist in transforming normal cells into immortal cells, which is one of the main features of cancer cells. At this point the regulation of telomeres and telomerase by HPV acquires an important role.

Thanks to the great variety of mechanisms that viruses use to infect cells, they are becoming a great tool to treat cervical cancer in order to avoid cases of relapse. In addition, those engineered viruses can control cell immortality. In summary, viruses play a dual role of cell immortality in cervical cancer. Then, the **main goals** of this review are:

- To explain the mechanisms of action by which HPV induces cell immortality in cervical cancer.
- To address the importance of the virus as a treatment of cervical cancer through the control of cell immortality.



Discussion

HPV oncoproteins alter cell cycle checkpoints

HPV-16 subtype is included in the high risk level, concretely; it is responsible of 50% of cervical cancers.

HPV-16 gene encodes some viral proteins. The most important oncoproteins are E6 and E7, which can deregulate cell cycle due to the lost of viral protein E2 that regulates these oncoproteins.

There are two main pathways that become modified: E6 oncoprotein with E6AP (ubiquitin ligase) can block TP53 pathway, and E7 oncoprotein can block pRB pathway. In both cases, this block is mediated by different mechanisms resulting in a high cell proliferation.

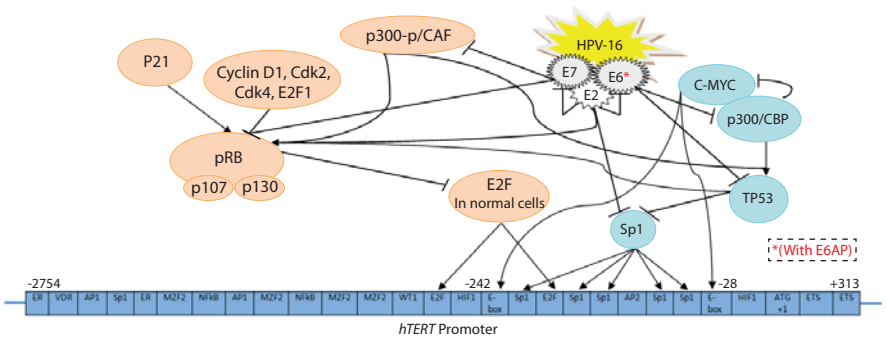
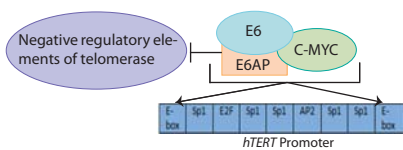


Figure modified from D. A. Skvortzov, et al., The Regulation of Telomerase in Oncogenesis. Acta Naturae, 2009.

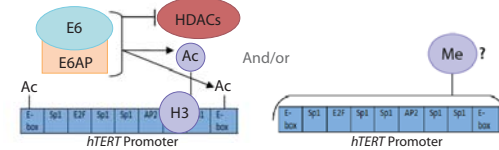
HPV monitors cell immortality through hTERT regulation. It can activate telomerase expression at different levels (A, B, C and D). In addition, HPV may down regulate telomerase activation by E2.

A balance between negative and positive regulation ways exists for viruses which require a latent infection. Activated telomerase ensures that infected cells can proliferate and avoid apoptosis. However, repression could prevent an immune response or create a state of transient genetic instability. The reason of why and when each mechanism is actuating remains unclear.

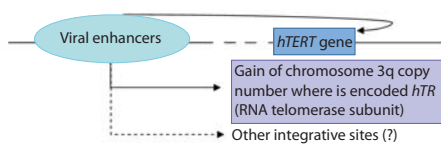
A. Trans-activation model



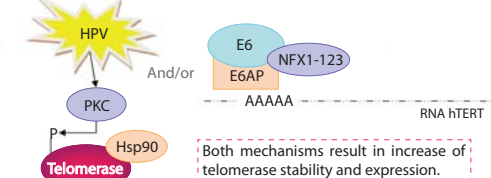
B. Epigenetic model



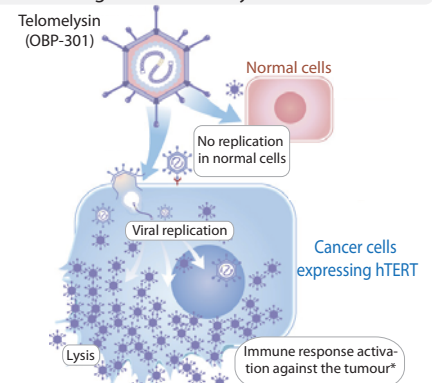
C. Cis-activation model



D. Post-transcriptional regulation model



Oncolytic virotherapy uses virus properties to destroy cancer cells. Best construct to the date to control cell immortality is telomelysin. It derives from an adenovirus (Ad5) and is regulated by hTERT expression. This construct induces death only in those cells that express hTERT subunit of telomerase. Telomelysin remains to be tested in cervical cancer but it has been demonstrated that reduces tumour size controlling cell immortality.



*Could be a disadvantage in case of readministration.

Figure modified from <http://www.oncolys.com/en/pipeline/obp-301.html>

Conclusions

(i) Cell immortality is associated with telomerase activation in cervical cancer. This review offers a global vision of the different mechanisms that HPV uses to control telomerase expression, usually, through hTERT subunit.

(ii) With some improvements, telomelysin (OBP-301) could allow scientists to control cell immortality in order to reduce tumour growth. Additionally, the use of OBP-301 would be a good therapy since it appears to enhance the immune response of the patient against the tumour.

Future approaches

- Knowing the different action mechanisms of HPV on the expression of telomerase, it would be great to enhance modified viruses to block these pathways.
- Apply the use of OBP-301 in cervical cancer in order to block telomerase expression and induce cell death.